Striatal sensitivity to reward deliveries and omissions in substance dependent patients

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A B S T R A C T

Some motivational theories of substance dependence (SD) posit either pathologically increased or decreased ventral striatum (VS) recruitment by cues for nondrug rewards. The incentive-sensitization hypothesis, alternatively, attributes SD to enhanced incentive salience of drug-predictive cues specifically, with no requirement for altered nondrug incentive processing. We assessed whether individuals undergoing inpatient therapy for SD are characterized by altered recruitment of mesolimbic incentive neurocircuitry by cues and deliveries of nondrug rewards. During functional magnetic resonance imaging, substance-dependent patients (SDP) and controls performed a modified monetary incentive delay task featuring: a) anticipatory cues that signaled opportunities to respond to a target to either win money or avoid losing money, b) notifications of wins and losses, and c) unexpected replacement of reward trial outcomes with a demand to repeat the trial. Both anticipatory reward cues and loss cues elicited similar mood responses and VS activation between SDP and controls. However, in SDP (but not controls), reward notifications also activated VS and mesial frontal cortex, and loss notifications activated anterior insula. Finally, substitution of expected outcomes in reward trials with notifications to repeat the trial deactivated the VS in SDP but not in controls. These data do not suggest that SD is characterized by altered recruitment of VS circuitry by cues for nondrug incentives. Rather, SDP may instead have increased limbic system sensitivity to reward and loss delivery, consistent with the role of impulsivity in SD.

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Introduction

The ventral striatum (VS), including nucleus accumbens (NAcc) has been established as a key node in neural circuitry underlying incentive salience or "wanting" of goal-objects (Knutson and Cooper, 2005; McClure et al., 2004b; O'Doherty, 2004). Although there is considerable evidence that the VS is highly responsive to drug associated cues among abusers (Braus et al., 2001; Grusser et al., 2004; London et al., 1999; Myrick et al., 2004; Sinha and Li, 2007), it is not clear how the VS of individuals with substance dependence (SD) responds to cues predictive of nondrug reward. In fact, motivation-based theories of SD etiology make differing predictions as to how individuals with SD might differ from controls in VS recruitment by cues for nondrug reward.

The reward deficiency syndrome (RDS) hypothesis (Blum et al., 2000) posits that individuals prone to addiction have a deficit in recruitment of dopaminergic-(DA) motivational circuitry by nondrug rewards, such that abused drugs are uniquely able to normalize DA levels in the VS to readily motivate drug-taking behavior. The allostatic

hypothesis (AH) (Koob et al., 2004), further posits that the neuro-chemical sequelae of chronic drug use itself also causes mesolimbic incentive neurocircuitry to become under-responsive to stimuli signaling availability of nondrug rewards (Koob and Le Moal, 2005). This pharmacologically induced anhedonia contributes to a general-ized dysphoric mood syndrome. Drug use temporarily restores the user's ability to experience pleasure while at the same time progressively-lowering a homeostatic set-point for positive emotion. Notably, alcohol (Schulteis et al., 1995), nicotine (Epping-Jordan et al., 1998), heroin (Kenny et al., 2006), amphetamine (Lin et al., 1999), or cocaine (Markou and Koob, 1991) withdrawal all raise the threshold of electrical current required to elicit mesolimbic self-stimulation in rodents. Accordingly, substance-dependent patients (SDP) might show subnormal activation of the VS by cues signaling availability to respond for nondrug rewards, either by virtue of a premorbid factor or due to chronic drug effects on the VS. A recent study showing reduced VS activation by reward-anticipatory cues in the monetary incentive delay (MID) task among alcoholics (Wrase et al., 2007) supports the RDS hypothesis.

Conversely, an opponent-process theory of SD posits that addic-tion-prone individuals are characterized by severe trait impulsivity resulting from some combination of overactive mesolimbic reward-approach circuitry and deficient frontocortical punishment–avoidance

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circuitry (Bechara, 2005; Bickel et al., 2007; Newman and Wallace, 1993). Large-scale twin studies indicate that a heritable, core impulse-control deficiency underlies the comorbidity between SD and other externalizing behavior disorders (Kendler et al., 2003; Kreek et al., 2005; Slutske et al., 1998). Indeed, SDP show impulsive (Bickel and Marsch, 2001) and reward-centric (Bechara et al., 2001) choice behavior in the laboratory. Moreover, individuals with alcohol (Bjork et al., 2004a) and cocaine (Heil et al., 2006) dependence show increased preference for immediately-presented rewards over larger but delayed rewards, and the availability of an immediately-reinforced choice activates VS relative to choices between two delayed rewards (McClure et al., 2004a). Were the opponent-process theory correct, SDP may show *increased* VS responsiveness to anticipatory cues for potential rewards. Alternatively, since decision-making of SDP is disproportionately influenced by the salience of recent (Yechiam et al., 2005) reward deliveries compared to punishments in laboratory tasks (Lane and Cherek, 2000; Stout et al., 2004), SDP may show increased striatal responsiveness to reward *outcome* notifications by virtue of trait impulsivity. Recent work showing that reward notification-elicited activation of the VS correlated positively with both psychometric (Forbes et al., 2007) and behavioral (Hariri et al., 2006) measures of impulsivity in healthy adults supports the idea that VS sensitivity to reward notification is a marker for impulsivity.

The incentive salience hypothesis (ISH) (Robinson and Berridge, 2001), on the other hand, attributes compulsive drug use to alterations of striatal circuitry that is normally recruited during associative learning. Drug-associated cues putatively acquire increased incentive-motivational salience irrespective of any changes in the hedonic experience of drug consumption itself. One mechanism for this has been proposed (Redish, 2004) wherein DA release in the VS following administration of abused drugs overrides the attenuation of reward-delivery-elicited DA release that normally occurs once an association between a reward-predictive cue with its subsequent delivery has been formed. This ostensibly causes an "over-learning" of the drug-predictive cue. Although increased incentive salience of drug-predictive cues (per the ISH) could occur in tandem with a general suppression of VS recruitment by nondrug rewards to produce a strong bias toward drug-taking, the ISH itself need not invoke any expectation of altered VS recruitment by nondrug reward-predictive cues. Potentiated VS responsiveness to drug cues alone might sufficiently bias behavior toward drugs. Were subjects with and without SD to show similar recruitment of VS by cues to respond for nondrug rewards, it would suggest that SD results from adaptations in responsiveness to drug cues in particular and not a more general alteration in VS cue responsiveness.

To address these hypotheses, we compared substance-dependent patients (SDP) and controls using an enhanced version of the monetary incentive delay (MID) task. The original MID task (Knutson et al., 2001) featured contiguous trials, wherein the anticipatory cues and the trial outcome notifications were closely and time-invariantly yoked, likely compromising independent deconvolution analyses of anticipation and outcome. Adding a jitter in the MID task between each of: cue and target, target and feedback, and between feedback and the cue of the subsequent trial facilitated separable deconvolution of response-anticipatory activation versus reward-notification activation (Dillon et al., 2008). We adopted within- and between-trial jittering to better detect whether the limbic system of SDP might show increased sensitivity to *notifications* of rewards. In decision-making studies, SDP show increased susceptibility for recent reward deliveries to bias behavioral choice (Lane and Cherek, 2000; Stout et al., 2004; Yechiam et al., 2005). Might this result from an exaggerated VS response to reward notification? Moreover, since SDP are characterized by increased trait neuroticism (Mulder, 2002), where neuroticism is defined by increased affective sensitivity to aversive stimuli (Costa and McCrae, 1992), might SDP show an exaggerated

limbic contrast between notification of success versus failure to either win rewards or to avoid losses?

In addition, we wished to stress the motivational system by providing an experience of frustration on some trials. Thus some reward trial outcomes were pseudorandomly omitted and replaced by a notification that the subject would have to repeat the entire trial to possibly obtain its reward. These double-response trials enabled within- and between-subject comparisons of anticipatory activation by informative cues (presented with no specific expectation of frustration) versus the same cues repeated following a dashed expectation of immediate reward. Using this approach, we hoped to determine whether SDP and controls differ in VS recruitment when the instrumental behavior requires greater persistence in the face of frustration. Lack of persistence as a personality trait is one facet of impulsivity (Smith et al., 2007), and has been characteristic of detoxified alcoholics who report more craving (Tavares et al., 2005), and who eventually relapse (Cannon et al., 1997).

Based on preliminary findings consistent with the RDS (Wrase et al., 2007), we hypothesized that SDP (here, detoxified inpatients being treated for alcohol dependence) would show reduced VS recruitment by reward-anticipatory cues of the MID task in this larger sample. Second, we hypothesized that SDP would show increased activation of VS and other limbic neurocircuitry by reward outcomes. Third, because increased negative affect is characteristic of alcoholics (Kessler et al., 1997; Mulder, 2002) and of illicit drug users (Kashdan et al., 2005), we predicted that omission of reward trial notifications with a demand for extra effort would result in increased reward frustration-elicited activation in limbic cortex of SDP (Siegrist et al., 2005).

Materials and methods

Subjects

Procedures were approved by the Institutional Review Board of the National Institute on Alcohol Abuse and Alcoholism. All subjects were right-handed. Subjects underwent physical examination and a structured clinical interview for DSM-IV. Exclusion criteria for all subjects were: current use of psychotropic medication, psychosis, craniofacial or soft-sign neurological evidence of fetal alcohol spectrum disorder (FASD), chronic medical conditions (e.g. diabetes), history of significant head injury, or of neurological disorder. The absence of illicit drug metabolites in urine was required for participation. Controls ($n=23$; age 22–46, mean 32.0 ± 8.0; 12 males) were recruited from community advertisement. Three controls were regular smokers. In controls, presence of any Axis I disorder was an exclusion criterion, as was a lifetime history of SD in any first-degree relative.

SDP ($n=23$; age 22–48, mean 34.0 ± 8.2; 12 males) were inpatients undergoing treatment for alcohol dependence at the National Institutes of Health in Bethesda, Maryland. All SDP met DSM-IV criteria for alcohol dependence. As part of FASD screening, SDP performed block design and vocabulary tests to detect mental retardation. All SDP had an estimated IQ≥80. The broader term SDP is used to designate patients in this report because every patient reported some history of use of illicit drugs, and every patient was a regular smoker. Twenty patients met DSM-IV criteria for current or lifetime abuse of or dependence on non-alcohol drugs. Comorbid diagnoses and abstinence duration of each SDP is listed in Table S1. In particular, seven SDP currently met criteria for comorbid cocaine dependence, and three other SDP met criteria for each of cocaine abuse, marijuana abuse, and hallucinogen abuse, respectively. In addition, five other SDP met criteria for past cocaine dependence, another SDP for past marijuana abuse, another for past marijuana dependence, and another for past cocaine abuse. Most SDP with some history of non-alcohol substance use disorder abused multiple illicit

drugs. Each SDP, however, cited alcohol as his or her drug of choice, and implicated alcohol as the primary cause of addiction symptomatology. In preliminary telephone intake interviews with a social worker, prospective patients who endorsed illicit drug use but who did not describe alcohol as their drug of choice were not admitted. Subsequently, any inpatient who exhibited a "cocaine crash" or other evidence that a non-alcohol drug was his or her primary problem was excluded. SDP were scanned after at least six days of drug abstinence (range 6–26; mean 12.34±5.3), as verified by analyses of urine and breath samples.

Monetary incentive delay task

Stimuli were back-projected on a screen at the foot of the scanner bed and viewed using a head coil mirror. Pseudorandomly-presented trials consisted of: cue presentation, target presentation, and either success-dependent feedback or notification of the requirement to repeat the trial (Fig. 1). All task stimuli within a trial, as well as the trials themselves (intertrial intervals), were separated by presentation of a fixation crosshair for a pseudorandomly jittered and uniformly-distributed duration of either 2, 4, or 6 s. This range of jitter intervals was chosen to both enable separable deconvolution of cue-elicited and notification-elicited activation while still retaining the contiguity of events (core structure) of the MID task while presenting enough trials within a scanning session of tolerable duration (~29 min) for patients.

First, a cue shape was presented for 250 ms, which signaled what the subject would win for hitting a target: either low-reward (50¢; 27 trials total, divided across three task runs), high-reward ($5; 27 total trials) or no reward ($0; 27 total trials). Subjects were instructed to respond to every target. Second, the cue was replaced by a crosshair for a variable, jittered interval (2, 4, or 6 s between onset of cue and onset of target). Third, a white target square was briefly presented (for 180–450 ms). To succeed on the trial, the subject was required to press a button on a button box while the target was on-screen.

After a jittered interval (2–6 s), this sequence concluded with a 2 s presentation of either: a) feedback of whether the subject hit the target (single-response trials; $n = 18$) or b) the word "Again!" which

notified the subject that the cue and target for the trial would be re-presented before an outcome would be delivered (double-response trials; $n = 9$). In each double-response trial, the same cue and target duration were repeated after pseudorandom 2–6 s delays, and were followed by 2 s feedback. In double-response reward trials, hits on both the first and second target were required to obtain reward.

Finally, to characterize activation by active avoidance and notification of losses, we also included trials where a striped square cue (250 ms) signaled the possibility of losing $5 (18 total trials divided across three task runs) if the subject failed to respond to the subsequent target while it was presented. Loss-avoidance trials were single-response only.

Prior to scanning, subjects were shown an envelope containing the cash they could win, and were read an instruction script describing the reward or loss consequences signaled by each of the four anticipatory cues. Subjects were briefed that in some trials, they would be required to respond to the target a second time, where in reward trials, hits on both targets were required to receive the reward. Then, during a 5-min practice session, reaction times to targets were covertly measured, and the distribution of target presentation durations was rigged so that each participant would succeed on ~66% of trials during the scan. In the scanner, each participant performed three runs of the task.

Psychometric measures

The NEO Personality Inventory (NEO-PI-R) (Costa and McCrae, 1992) was administered to 17 controls and 19 SDP prior to scanning. To limit comparisons, incorporation of NEO data was restricted to two scales. First, since many SDP had histories of primary or secondary mood disorders, NEO-neuroticism factor scores were included in *post hoc* analysis to control for greater negative affect in SDP. Second, the 8-item impulsiveness facet score of the NEO was calculated to enable *post hoc* exploration of whether recruitment of mesolimbic circuitry by incentive cues or deliveries directly related to an approximation of trait impulsivity (Forbes et al., 2007) irrespective of SD. Immediately after scanning with the MID task, subjects rated on four-point scales how "excited," "happy," "fearful," and "unhappy" they felt when they
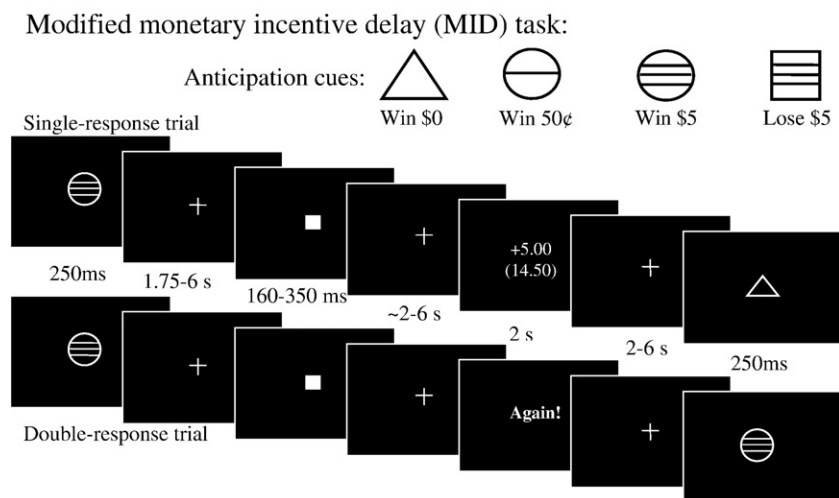

Fig. 1. Modified monetary incentive delay (MID) task. In each trial, subjects were initially presented with one of four anticipatory cues followed by a fixation crosshair for a jittered duration (1.75–6 s), and a target followed by a post-target fixation crosshair for (~2–6 s). Subjects were required to respond during target presentation ("hit") to either win money, avoid losing money, or for no consequence. In single-response trials, subjects then viewed notification of whether the target was hit or not, followed by a jittered (2–6 s) intertrial interval with fixation crosshair. In double-response trials (33% of win $0, win 50¢, and win $5 magnitudes), notification of trial outcomes were pseudorandomly replaced with the word "Again!" which notified the subject that he or she must repeat the trial to obtain an outcome. This was followed by: a jittered (2–6 s) fixation crosshair, a second presentation of the same incentive cue, a jittered (1.75–6 s) post-cue fixation crosshair, target presentation of the same duration, jittered (~2–6 s) post-target fixation crosshair, and 2 s outcome notification, where hits on both targets were required for trial success.

saw each type of task cue. Affect ratings for incentive-laden cues were calculated and analyzed as the net difference from the subject's analogous rating of the non-incentive cue.

fMRI acquisition

Imaging was performed using a 3 T MRI scanner (General Electric, Milwaukee, WI) with an 8-channel head coil. Functional scans were acquired using a T2*-sensitive echoplanar sequence with TR= 2000 ms, echo time=30 ms, flip=90°. We collected 24 4.0 mm thick sagittal slices. In-plane resolution was 3.75×3.75 mm. Structural scans were acquired using a T1-weighted sequence for coregistration of functional data. Each subject's head was restrained with a deflateable head cushion.

fMRI analysis

Preprocessing

Blood Oxygen-Level Dependent (BOLD) signal was analyzed using Analysis of Functional NeuroImages (AFNI) software (Cox, 1996). Voxel time series were interpolated to correct for nonsimultaneous slice acquisition, then corrected for head motion. No participant's head moved more than 1.5 mm in any dimension between volumes or more than 3 mm overall. Data were spatially smoothed with an 8 mm FWHM isotropic kernel, followed by a despiking algorithm and bandpass filtering of cyclical fluctuations in signal not indicative of a hemodynamic response (either greater than 0.011/s or less than 0.15/s). Time series data were then normalized as percent signal change from mean.

Individual subject statistical maps

Time series datasets were analyzed with multiple regression. Regressors of interest were modeled with canonical gammavariate hemodynamic response functions (HRF) time-locked to the presentation of: a) anticipatory cues, b) "Again!" and c) notification of outcomes (hits and misses modeled separately). Additional regressors controlled for residual head motion, as well as baseline and linear trends. Activations were then detected by linear contrasts (LC) between: a) anticipation of responding for all rewards (50¢ and $5) versus nonincentive ($0) in single-response trials and in the first response of double-response trials (consolidated because subjects never knew when an initial cue and target would be followed by an actual outcome), b) anticipation of responding to avoid losses ($5) versus nonincentive ($0), c) feedback of successful versus unsuccessful outcomes in single-response reward trials, and d) feedback of losses versus avoided-losses in the loss-avoidance trials. To detect reward omission activation, in reward trials, "Again!" notifications were contrasted with notification of non-wins. Both trial types would have identical anticipatory activity and absence of reward delivery, but would differ in the potential of frustration by the requirement to repeat the trial despite possibly having responded appropriately.

Groupwise statistical maps

Individual statistical maps of linear contrast activations were warped to Talairach space. These were consolidated using the AFNI plug-in module 3dANOVA2. The ANOVA model featured subject group as the group-identification and comparison variable of interest, and included an individual subject variable as a random effect of no interest. Activations in groupwise consolidated maps are reported as the maxima of clusters, where voxels singly activated to a statistical significance threshold of $p<.001$ comprised a contiguous cluster of sufficient volume (≥23 voxels, or ~1.29 ml) to obtain a family-wise corrected type I error rate ≤0.05 using Monte Carlo simulation. In regions with suprathreshold activations, we conducted *post hoc* voxelwise between-group t-tests (see Supplemental methods).

Volume-of-interest (VOI) analyses

BOLD signal data in the VS were analyzed in 5 mm-diameter spherical masks localized *a priori* in the nucleus accumbens (NAcc) (Talairach left: −10 10 −4; right: 10 10 −4). This mask was located at the ventromesial intersection of caudate and putamen (Fig. 4a) in the coronal plane. Reward anticipation and feedback activation have been reliably elicited by this paradigm at this location (Bjork et al., 2004b; Knutson et al., 2001, 2005; Scheres et al., 2007). Masks were individually re-positioned up to 2 mm to ensure placement in gray matter. Signal change was also characterized in 5 mm radius spheres localized *post hoc-* at the maxima of reward-outcome-elicited activation in mesial frontal cortex (0 46 3) and loss-outcome-elicited activation in left anterior insula (−34 18 2) in SDP. Event-averaged data were baseline-corrected as the difference from signal measured during stimulus presentation. Signal and behavioral data were characterized by repeated-measures, mixed-model analyses of variance (rmANOVA) (see Supplemental methods).

Results

Task behavior and questionnaire responses

In all trial types, SDP responded to targets significantly faster than controls (Fig. S1). Controls (but not SDP) responded more quickly to targets as incentive magnitudes increased. Controls and SDP also responded faster to second targets relative to first/only-response targets, due primarily to faster responses to second targets in nonincentive double-response ("Again!") trials. Across runs (1–3) of the task, subjects responded more slowly to nonincentive targets.

Due to individually-customized task difficulty, RT differences did not translate into group differences in hit rates. In single-response reward trials, there was a trend ($F(1,44)=2.949$; $p<.10$) for subjects to hit more targets in the high- (69.6%) compared to low- (65.9%) magnitude trials, with no main or interaction effects of group on hit rates. In double-response reward trials, subjects successfully hit both targets in 56.0% for low-reward, and 57.2% for high reward, with no main or interaction effects of magnitude or group. Critically, there were no group differences in incidence of failure to hit first targets of double-response reward trials ($p>.8$), thus minimizing likelihood of a group difference in expectation of reward. Subjects avoided loss in 74.8% of loss-avoidance trials, with no group difference. Nonincentive cues elicited more fearfulness in SDP (see Fig. S2), but there were no group differences in affective responses to any other cue, nor in self-reported affective responses to "Again!" notifications. NEO-neuroticism scores and NEO-impulsiveness scores were significantly higher in SDP (neuroticism — controls: 39.2 (±16.0), SDP: 52.8 (±14.1), t-test $p=.01$; impulsiveness — controls: 44.1 (±5.6), SDP: 57.7 (±5.9), $p<.001$).

Linear contrast-derived brain activations

Reward versus nonreward anticipation

Anticipation of responding for reward (50¢ and $5 magnitudes collapsed) versus responding for no incentive activated the VS bilaterally in both SDP and controls, with activation extending into anterior insula (Table S2; Figs. 2a, b). Both groups also showed activation in posterior mesofrontal and superior parietal cortices, with additional mesial occipital activation in controls. Voxelwise ANOVA indicated no significant group difference in VS activation by reward anticipation.

Loss versus nonloss anticipation

Anticipation of responding to avoid loss versus responding for no incentive bilaterally activated caudate, putamen, and anterior insula as well as posterior mesofrontal and occipital cortices in both SDP and controls (Table S3; Figs. 2c, d). Voxelwise ANOVA
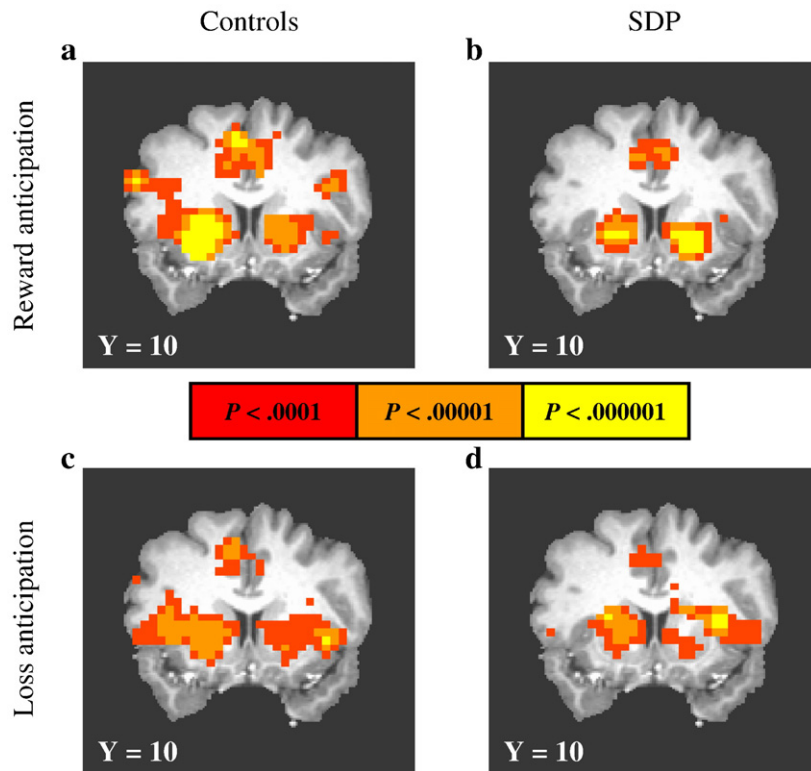
Fig. 2. Activation by anticipation of rewards and losses. Anticipation of responding for rewards (50¢, $5) contrasted with anticipation of responding for no incentive activated bilateral ventral striatum in controls (a), and SDP (b), with no voxelwise group differences in anticipatory activation. Anticipation of responding to avoid losses ($5) contrasted with anticipation of responding for no incentive activated insula and bilateral dorsal striatum in both controls (c), and SDP (d), with no voxelwise group differences in anticipatory activation. Brain images in this and subsequent figures are right–left reversed per radiological convention, and are derived from a T1-wieghted scan of a representative control subject at the planar Talairach coordinate shown. Color overlays depict uncorrected voxelwise *p* statistics, where warm colors denote activations and cool colors denote deactivations.

indicated no significant group difference in VS activation by loss anticipation.

Reward versus nonreward outcomes

In SDP, but not in controls, feedback of reward versus failure to win reward activated the VS bilaterally as well as mesial frontal cortex and supragenual anterior cingulate cortex. In controls, reward notification activated only occipital cortex (Table S4; Figs. 3a, b). In the voxel-wise ANOVA, SDP had significantly greater activations than controls in right NAcc, left anterior insula, and in mesofrontal cortex (Fig. 3c).

Loss versus loss-avoidance outcomes

One SDP successfully avoided all potential losses and is excluded from this analysis. Notification of losses (contrasted with loss avoidance) activated left anterior insula and thalamus in SDP (Table S4; Figs. 3d, e). There was no suprathreshold activation by this contrast in controls. Accordingly, SDP had significantly greater activation by loss notification in anterior insula, with relatively increased activation extending from left anterior insula into lateral frontal cortex (Fig. 3f).

"Again!" versus non-reward outcomes

Notification of the requirement to repeat the operant response for reward versus actual notification of failure to win reward (in single-response trials) activated occipital and superior temporal cortex, and deactivated anterior cingulate cortex in both SDP and controls (Table S5; Figs. 3g, h). "Again!" notifications also deactivated VS bilaterally in SDP. This deactivation of bilateral VS with "Again!" notifications versus notification of failures to win reward was of greater magnitude in SDP compared to controls (Fig. 3i).

Although there was no group difference in activation by a linear contrast between reward versus nonreward anticipation, a pathological difference in VS activation by either reward or loss cues in SDP may have been masked in a linear contrast by a similar groupwise difference in activation by nonincentive cues. We calculated and compared *post hoc* the group-maps of each task event (reward cues, loss cues, nonincentive cues, wins, non-wins, losses, nonlosses, and "Again" notifications) modeled singly. These indicated: 1) no voxelwise group differences in VS activation by any of reward cues, loss cues, or nonicentive cues, 2) no voxel-wise differences in deactivation of VS by notification of nonwins in reward trials, 3) increased activation of VS by actual low and high reward wins in SDP, and 4) increased deactivation of VS by "again" notifications in SDP. These single-event findings are characterized statistically and graphically in a VOI analysis (below).

Stimulus-elicited signal change in VOI

VOI analyses are limited to characterization of activations revealed by the linear contrasts. Preliminary analysis indicated similar stimulus response between right and left NAcc.

Reward anticipation activation in NAcc

Anticipatory cues elicited hemodynamic responses in the NAcc that increased with incentive magnitude in both groups to a similar extent (Fig. 4). NAcc responses to the repeated cue in double-response trials, however, were similar across magnitudes. A significant magnitude × time interaction illustrated that cue-elicited signal change increased with incentive magnitude (both first- and second-attempts collapsed; $F(10,440)=6.714$, $p<.000001$). A significant attempt × time effect ($F(5,220)=5.300$, $p<.001$) indicated increased signal change anticipating the second response across all incentives. A
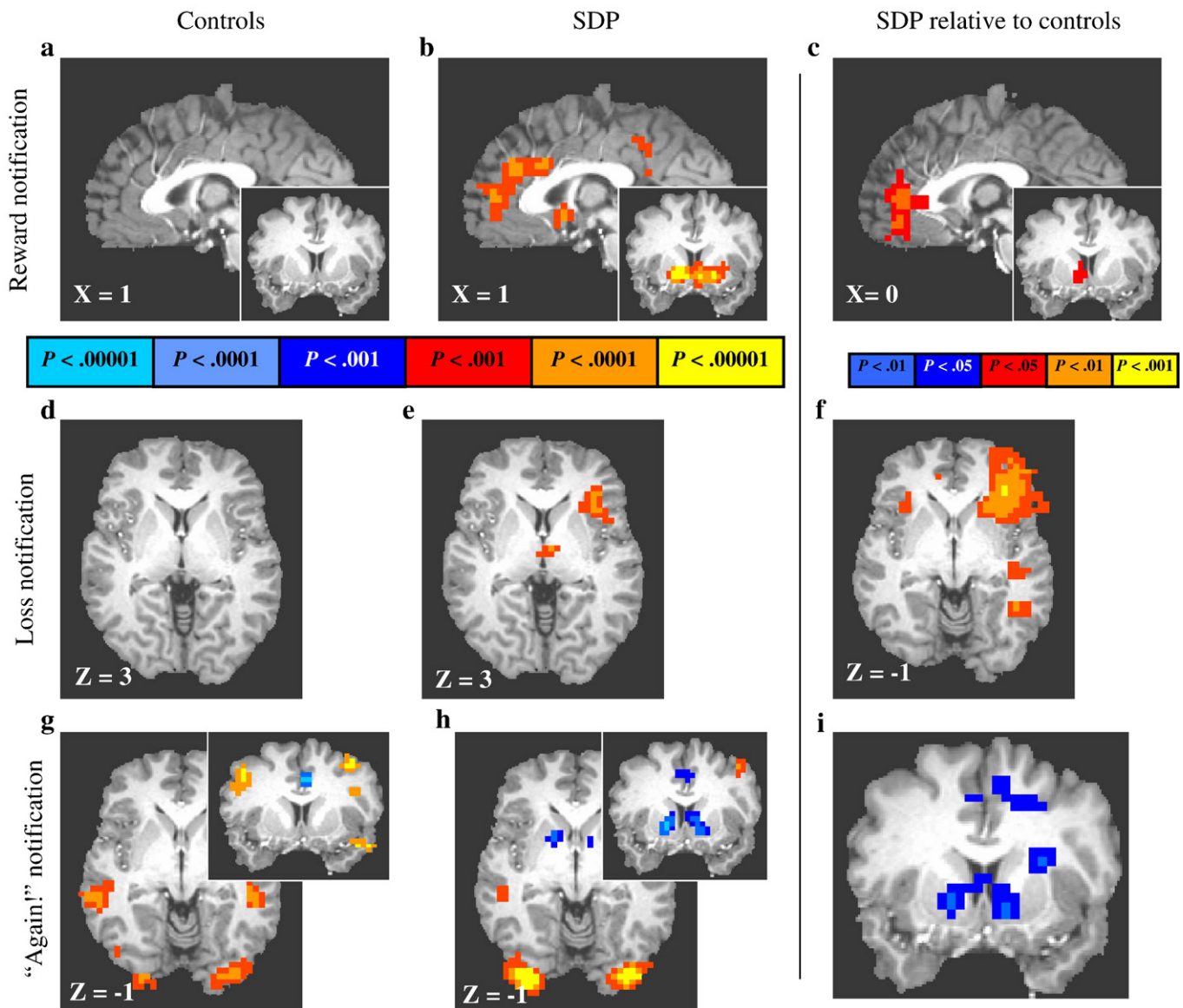
Fig. 3. Activation by notification of rewards, losses, and omission of outcomes. Notification of rewards (50¢, $5) contrasted with notification of failure to win reward did not activate mFC and VS in controls (a), but activated both regions in SDP (b). The voxelwise group difference in mFC and VS activation was significant (c; SDP>control activation depicted in warm colors). Notification of losses ($5) contrasted with notification of loss-avoidance did not activate any region above threshold in controls (d), but activated thalamus and anterior insula in SDP (e). The voxelwise group difference in insula activation was significant (corrected $p<.05$) (f). Replacement of outcome notification with the demand to repeat the trial effort ("Again!") in reward trials (50¢, $5) contrasted with notification of nonwins in single-response reward trials activated temporal, occipital, and dorsolateral frontal cortex in both controls (g) and SDP (h), with additional suprathreshold deactivation of VS (cool colors) in SDP. The voxelwise group difference (corrected $p<.05$) in VS deactivation was significant (f; SDP deactivation>control deactivation depicted in cool colors). All coronal inset images are at $y=9$.

significant magnitude×attempt×time effect ($F(10,440)=6.364$, $p<.000001$) resulted from attenuated cue-elicited signal change from first to second attempts for high rewards (attempt×time effect ($F(5,220)=6.123$, $p<.0001$) but increased cue-elicited signal change from first to second attempts for no incentive (attempt×time effect ($F(5,220)=4.852$, $p<.001$). There were no main or interaction effects of subject group on reward-anticipatory activations.

Loss anticipation activation in NAcc

NAcc responses to cues to avoid a $5 loss were similar to responses to win gains, and also activated the NAcc more than did nonincentive cues (Fig. 4b; magnitude×time interaction $F(5,220)=28.853$, $p<.000001$. This did not further interact with subject group. When directly comparing hemodynamic responses to cues for $5 gains versus $5 losses, there was no significant valence×time interaction effect on signal change, nor interaction effect of group.

Reward notification activation in NAcc and mFC

Winning money activated the NAcc and mFC in SDP, but not in controls (Fig. 5). Conversely, notification of failure to win money deactivated the NAcc and mFC (outcome×time interaction NAcc ($F(5,220)=5.777$, $p<.0001$) and mFC ($F(5,220)=6.975$, $p<.00001$), and this did not further interact with group. In rewarded trials analyzed separately, however, a significant time× group interaction indicated notification-elicited signal increases specific to SDP in the NAcc ($F(5,220)=3.868$, $p<.01$). In non-rewarded trials, there was no time×group interaction effect on signal change.

Loss notification activation in anterior insula

Notification of losses activated left anterior insula in SDP but not in controls. First, a significant outcome×time interaction effect (both subject groups collapsed; $F(5,215)=2.906$, $p<.05$) indicated greater
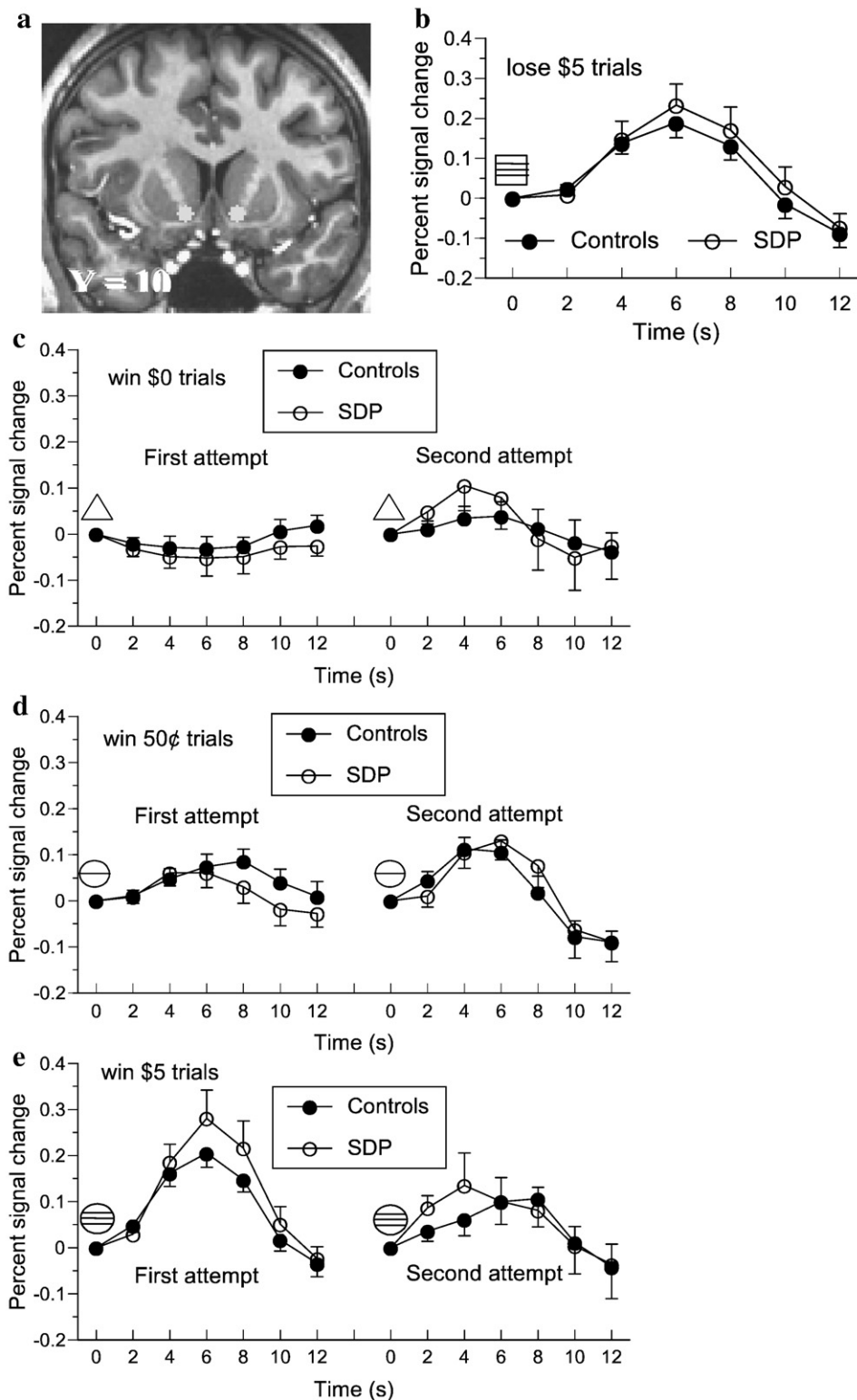
Fig. 4. Anticipation cue-elicited signal change in NAcc VOI. In a VOI drawn in the NAcc bilaterally (Talairach ±10 +10 −4; part a), both controls and SDP showed similar BOLD signal increases anticipating losses (b). Across nonincentive (c) and reward (d,e) trials, a significant magnitude×attempt×time interaction effect ($p<.05$) indicated magnitude-sensitive anticipatory activation in first attempts (single-response trials plus first attempts in double-response trials), but similar anticipatory responses across magnitudes in the second attempts of double-response trials. Simple effect tests indicated no group difference in signal change at any post-cue timepoint.

signal increases following notifications of losses relative to non-losses in left anterior insula (Fig. 5e). The outcome×time×group interaction effect ($F(5,215)=3.675$, $p<.01$), however, indicated that loss-elicited insula recruitment was specific to the SDP.

"Again!" notification activation in NAcc

The substitution of reward trial outcomes with the command "Again!" deactivated the NAcc in both groups (Fig. 5f), similar to the NAcc deactivation by notification of non-win outcomes. A trend for a
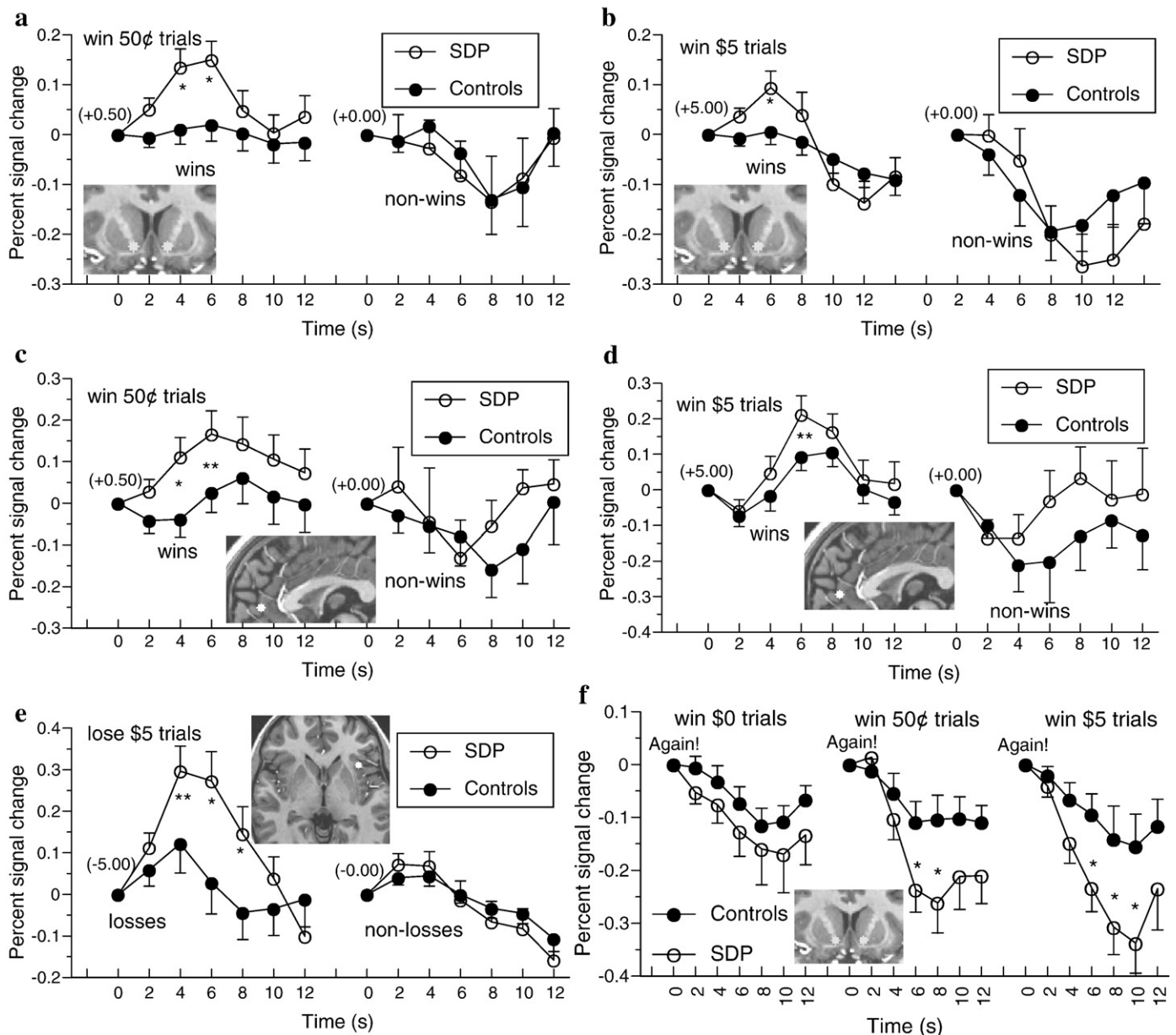
Fig. 5. Outcome-elicited signal change in VOI. In the NAcc VOI, SDP but not controls showed signal increases in response to notification of low (a) and high (b) rewards in single-response trials. Signal decreases following notification of failure to win reward were similar between groups. In the mFC VOI drawn at the win versus non-win LC maxima of SDP (Tlrc: 0 46 3) (c and d insets), SDP also showed a trend for greater signal increases in response to notification of low (a) and high (b) rewards in single-response trials. In the left insula VOI drawn at the loss versus non-loss LC maxima of SDP (Tlrc: 34 18 2) (e inset), SDP showed greater signal increases following notification of losses (e) with similar response to controls following non-losses. When outcomes were unexpectedly deferred, SDP and controls showed similar signal decreases following "Again!" notification to repeat trials in non-incentive double-response trials (f, left-most plot). However, SDP showed greater deactivation in response to outcome omission in low (center plot) and high (right-most plot) reward double-response trials. Groupwise differences are denoted as * $p<.05$ and ** $p<.10$.

magnitude×time interaction effect (both groups collapsed; $F(10,440)$ =1.745, $p<.10$) indicated greater signal decrease in NAcc as the magnitude of expected gains increased. Unlike with non-win outcome notifications, however, "Again!"-elicited NAcc deactivations were more pronounced in SDP (time×group interaction effect ($F(5,220)$= 2.380, $p<.05$).

Psychometric correlates of event-related activation in VOI

We probed VOI data to ascertain: 1) whether individual differences in positive affect elicited by high-reward cues related to response-anticipatory NAcc recruitment as in previous experiments, and 2) the

degree to which the larger outcome-elicited limbic activations in SDP related to their greater questionnaire impulsivity and neuroticism (negative affect).

Anticipatory activations

Individual differences in peak high-reward anticipatory NAcc signal change (averaged across 4 s and 6 s lag timepoints following cue) correlated with net self-reported excitement elicited by the high reward cue in controls (Spearman $r=.570$, $p<.01$; Fig. 6a) but not in SDP (Spearman $r=.233$, n.s.; Fig. 6b). Reward-anticipatory signal change did not correlate with net self-reported happiness, and loss-anticipatory signal change did not correlate with either
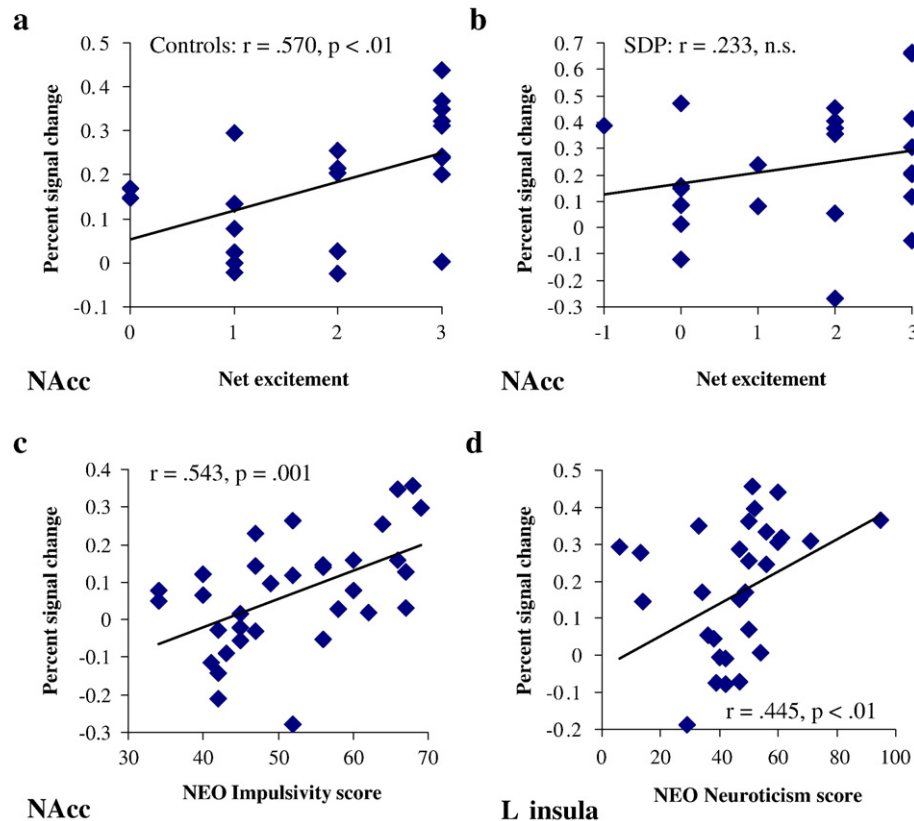
Fig. 6. Correlations between psychometric measures and signal change in VOI. Excitement and happiness ratings about high reward cues were calculated as the net difference from the subject's excitement/happiness about the non-incentive cue. In the bilateral NAcc VOI, individual differences in peak anticipatory signal change correlated with net self-reported excitement elicited by the high reward cue in controls (a) but not in SDP (b). Across all subjects, individual differences in NAcc response to notification of low (50¢) rewards correlated with NEO-impulsiveness scores (c), and individual differences in left anterior insula activation by notification of losses correlated with NEO-neuroticism scores (d).

unhappiness or fearfulness about loss-predictive cues. There were no correlations between reward- or loss-anticipatory NAcc signal change and either NEO-neuroticism or NEO-impulsiveness scores.

Notification-elicited activations

Across all subjects, peak NAcc responses to notification of low rewards correlated positively with individual differences in both NEO-impulsiveness (Spearman $r = .543$, $p = .001$; Fig. 6c) and NEO-neuroticism (Spearman $r = .389$, $p < .05$). To ascertain whether SDP still had greater NAcc responses to low rewards after controlling for their greater neuroticism and impulsivity, we performed *post hoc* regression analyses with group and either NEO-impulsiveness scores or NEO-neuroticism scores added as an independent variable (with low-reward-elicited NAcc signal change as the dependent variable). Adjusted mean signal increases were no longer elevated in SDP ($p > .75$). Rather, low-reward-elicited signal change partially correlated with each of NEO-impulsiveness scores (Beta = .567, $p < .01$), and NEO-neuroticism scores (Beta = .372, $p < .05$), after controlling for diagnostic group. NAcc recruitment by notification of high rewards or by losses, however, did not correlate with NEO-neuroticism or NEO-impulsiveness scores. Accordingly, peak NAcc responses to high reward notification remained significantly higher in SDP ($p < .05$) after controlling for NEO-impulsiveness and NEO-neuroticism scores, with no independent partial correlation between NEO measures and NAcc activation while controlling for group.

In the mFC VOI, NEO-impulsiveness correlated with recruitment by high- (but not low-) reward notifications across all subjects (Spearman $r = .358$, $p < .05$). Accordingly, high reward-elicited mFC activation was similar in SDP and controls ($p = .37$) after controlling for NEO-impulsiveness scores in multiple regression. mFC activation did not

correlate with NEO-neuroticism. Finally, in left anterior insula, loss-elicited activation correlated with NEO-neuroticism across all subjects (Spearman $r = .445$, $p < .01$; Fig. 6d). Accordingly, insula activation by losses was no longer greater in SDP ($p = .48$) after controlling for NEO-neuroticism scores in multiple regression.

Discussion

Main findings

Although most of these alcoholics also had lifetime histories of comorbid illicit drug use disorders (a severe psychiatric phenotype), their VS recruitment by reward-predictive and loss-predictive cues was substantially similar to that of controls. Self-reported affect elicited by the incentive-linked anticipatory cues was also similar between groups. In both groups, cue-elicited VS hemodynamic responses were sensitive to potential reward magnitude, but not when cues were repeated in double-response trials. In controls (but not SDP) VS recruitment by the high-reward cue correlated with net self-reported excitement about the high-reward cue, consistent with earlier reports (Bjork et al., 2004b; Knutson et al., 2001) using the MID task. In contrast, SDP showed significantly increased activation of VS and mFC by notifications of reward delivery as well as insula activation by notification of losses. Most group differences in notification-elicited signal change in VOI were eliminated after covarying for either the higher NEO-impulsiveness or higher NEO-neuroticism scores of the SDP. Finally, the unexpected replacement of trial outcomes with a demand to repeat the trial deactivated the VS, similar to VS deactivation by notifications of failure to win. These VS deactivations were significantly more pronounced in SDP, despite no group

difference in self-reported unhappiness about such notifications or in rates of first-target misses.

Cue-elicited response-anticipatory activation

These data did not replicate the VS reward-anticipation deficit found in the previous study of SDP who performed the original MID task (Wrase et al., 2007). In addition, unlike the Wrase study, SDP responded faster than controls did to targets across all incentive magnitudes of the task. We suspect that the intense vigilance and motor behavior demands of the traditional MID task (response required every 6 s), coupled with the greater mean age of SDP in the Wrase experiment (42.4 compared to 34.0 here) may have taxed the motivation and sustained attention of those SDP enough to reveal both a VS recruitment and RT decrement. Attentional performance itself is sensitive to manipulations of the VS (Pezze et al., 2007), and children (Scheres et al., 2007) and adults (Strohle et al., 2008) with attention-deficit hyperactivity disorder (ADHD) showed a VS activation deficit using more rapid MID tasks. Moreover, volumetric MRI studies demonstrate that alcoholism-induced potentiation of brain atrophy with aging accelerates in middle age (Pfefferbaum et al., 1992). These divergent behavioral and activation findings caution that characterization of pathophysiological differences in motivational neurocircuitry in addiction may be very sensitive (or specific) to behavioral task parameters and individual differences in patient characteristics.

The NAcc response to cues for uncertain $5 losses was similar to that for $5 gains in each of SDP and controls (Figs. 5b and e). This is in accord with recently-reported similar peak NAcc responses to anticipatory cues for (response-contingent) $3 gains versus $3 losses (Cooper and Knutson, 2008). These data support a partial role of behavioral salience in accounts for NAcc recruitment (Zink et al., 2004) in that high reward and loss cues were both equally "actionable" with regard to behavior-contingent net economic outcomes. In nonincentive and reward trials, the VS of both SDP and controls responded to the initial trial cues in a magnitude-sensitive manner, but VS recruitment did not significantly differentiate across incentives when the incentive cue was repeated following "Again!" notifications in double-response trials. We suspect that high-reward cues presented a second-time in double-response trials did not elicit as great a signal increase as initial high-reward cues because they were no longer informative about the stakes of the trial. Alternatively, this signal increase could have been blunted by previous decreases following "Again!" notifications, which were most severe in high-reward trials.

Notification-elicited activation

NAcc activation by the notification of *low* reward (here 50¢) was uniquely reflective of individual differences in each of: SD diagnosis, questionnaire impulsivity, and questionnaire neuroticism. We detected greater VS and mFC activation by reward deliveries in SDP, and we posit that much of this difference likely relates more broadly to the increased trait impulsivity and neuroticism characteristic of individuals with severe histories of SD. This group difference reflects a recent finding (Heinz et al., 2007) that compared to controls, alcoholics showed increased NAcc response to positively-valenced International Affective Picture System (IAPS) pictures (contrasted with neutral pictures). This VS activation by reward delivery in SDP (but not controls) is also similar to their idiosyncratic VS activation when they were accumulating guaranteed reward (versus non-rewarded motor behavior) in a risk-taking motivational task (Bjork et al., 2008).

The direct bivariate correlation between a questionnaire measure of impulsivity and reward notification-elicited VS recruitment is in accord with (Forbes et al., 2007). Given the role of the mFC (Knutson et al., 2003) and VS (Elliott et al., 2000) in processing relative valuation of

received rewards, these enhanced reward notification-elicited meso-limbic activations in SDP by token rewards may be a physiological signature of their reward-centric bias detected in decision-making studies (Lane and Cherek, 2000; Stout et al., 2004; Yechiam et al., 2005). Greater mesolimbic sensitivity to outcomes may also contribute to both motivational and emotional instability (such as reactive temperament) in SD. Critically, in a factor-analysis of multiple impulsivity and personality questionnaire responses (Whiteside and Lynam, 2001), the NEO-impulsiveness facet loaded most strongly onto an urgency factor, where "high scorers on urgency are likely to engage in impulsive behaviors in order to alleviate negative emotions despite the long-term harmful consequences of these actions" (p. 685). Inasmuch as such behavior is almost universally reported by our patients, the relationship between NEO-impulsiveness scores and limbic responses to MID task outcomes is highly clinically relevant.

It is also possible that the VS of the SDP may also have been hyper-responsive to reward deliveries not due to a differential affective reaction to rewards, but due to deviant temporal difference reinforcement learning (TDRL) circuitry (O'Doherty et al., 2003; Schultz, 2007) when attempting to discover their success on the task. Several fMRI studies report mesolimbic deactivations when expectancies of reward delivery are systematically violated (Berns et al., 2001; Haruno and Kawato, 2006; McClure et al., 2003; O'Doherty et al., 2003; Spicer et al., 2007), and also show that the VS is selectively activated in fMRI by uncertain rewards (Bjork and Hommer, 2007; Heekeren et al., 2007). Despite near-identical rates of success at hitting first targets in double-response reward trials, if the SDP were more uncertain of their success, reward deliveries may have violated greater expectations of non-wins, resulting in greater activation of the VS by rewarding outcomes. However, in "Again!" trials, when reward trial outcomes were unexpectedly deferred, NAcc BOLD signal decreased more severely in SDP. Were the SDP to have reduced expectation of reward deliveries after responding to the initial target, the prediction error signal (here, deactivation) would have *reduced* compared to controls. Future experiments that parametrically and bivalently violate reward expectancies in SDP are of interest.

That SDP demonstrated differential VS recruitment between notification of success versus failure in trial outcomes is in apparent contradiction with emerging findings in cognitive and decision-making literature, where SDP are typically characterized by blunted regional brain recruitment by (and behavioral adjustments following) task errors (Garavan and Stout, 2005). However, we note that the majority of other studies involve either a significant cue learning component, a heavy cognitive demand for accurate signal detection, or both. In contrast, the MID task entails neither. In this experiment, subjects were explicitly briefed of the trial contingencies signaled by the anticipatory cues, and did not have to choose or discriminate between stimuli that actually elicited responses. Subjects simply responded as quickly as possible to every white square target they saw. Finally, error-related activation deficits in SDP in previous studies have typically been reported in cortical regions such as anterior cingulate, in contrast to group-wise differences in VS signal change seen here. To explore this discrepancy, future studies of outcome-monitoring could factorially modulate motivational, sensory, and cognitive components within the task.

The VS of controls was not significantly responsive to reward notifications. This contrasts with previous findings using event-related incentive tasks that reported VS (Breiter et al., 2001) and caudate head (Delgado et al., 2004) recruitment by reward delivery in healthy controls. There are several potential reasons for this. First, considered in the context of the TDRL, the MID task may generally elicit expectations of reward in trials since it is custom-calibrated for subjects to succeed most of the time. Therefore, TDRL theory would predict minimal activation by successful reward obtainment when success is typical, but pronounced deactivation by reward non-delivery. Notably, across both reward amounts, VS *deactivation* in

response to non-wins was more prominent than VS activation by wins in VOI analysis. Second, recent event-related fMRI studies of reward delivery in controls indicate that appreciable reward delivery-elicited (net) signal increases in VS occurred only in roughly half of the subjects, and was specific to subjects with either high trait impulsivity scores (Forbes et al., 2007), or who severely discounted delayed rewards in a task outside the scanner (Hariri et al., 2006). It may be that our exclusion of potential controls with immediate family history of a SD selected for very low trait impulsivity and group-averaged signal change in controls. Third, in the majority of experiments that reported notification-elicited activation of the VS (including with the original MID task (Bjork et al., 2004b; Knutson et al., 2001)), outcomes were time-invariantly yoked to reward-predictive anticipatory cues. Here, the interval between anticipatory cues and notifications was jittered — up to 12 s. It may be that activations ostensibly attributed to reward notification in previous MID task experiments (by contrasting successful versus unsuccessful outcomes) were confounded by hemodynamic spillover from anticipatory activation in that subjects may have been more engaged in the task in some trials (with greater anticipatory NAcc activation), and were more likely to be successful in those trials. A methodological study featuring a within-subject comparison of outcome-elicited activation by different variants of the MID task could address these potential confounds.

Both groups showed insula activation in response to anticipatory cues, and notification of losses activated the left anterior insula in SDP, but not in controls. The anterior insula has been extensively implicated in the conscious, emotional processing of visceral somatic states (Paulus and Stein, 2006). Specifically, left-lateralized insula activation has been elicited by subjective experience of parasympathetically-driven peripheral physiological responses, while right insula activation has been elicited in conjunction with sympathetic peripheral physiological responses (reviewed in Craig, 2005). The insula has been previously recruited by task conditions involving uncertain outcomes, such as by choosing a risky response option in a decision-making task (Paulus et al., 2003). It is therefore not surprising that cues for potential (but uncertain) incentives would elicit a cortical signal of physiological arousal.

The greater left insula response to losses in SDP may have been a cortical correlate of exaggerated emotional processing of interoceptive stress responses (Paulus and Stein, 2006), where aberrant autonomic stress responses are also characteristic of many alcohol-dependent patients (Monforte et al., 1995). For example, right insula was recruited more heavily during decision-making tasks in persons with high NEO-neuroticism (Paulus et al., 2003) and was also activated by task errors more in subjects with high trait anxiety (Paulus et al., 2004). Similarly, left insula activation during discrimination of ambiguous facial stimuli correlated positively with psychometric scores of uncertainty intolerance (Simmons et al., 2008). Here, across all subjects, peak left insula response directly correlated with NEO-neuroticism scores. Of interest would be future incentive experiments that survey physiological measures in conjunction with the fMRI signal.

Study limitations and future directions

It is possible that the greater reward notification-elicited mesolimbic activations in SDP did not result from a pathophysiologically idiosyncratic response to instrumental reward deliveries, but instead resulted from greater valuation of even small amounts of money if patients tended to be poorer than controls. Since we did not collect quantitative measures of socioeconomic status, this cannot be ruled out. There are several factors, however, that argue against this confound. First, SDP and controls reported similar affective reactions to the prospect of winning, and also showed similar response-anticipatory NAcc activation by low- and high-reward cues. These findings suggest similar motivation to respond. Second, SDP

responded more quickly than controls to nonincentive targets, not just to incentive-laden targets. Third, in a recent experiment, cocaine abusers did not generally differ from controls in their subjective valuation of a range of monetary amounts (Goldstein et al., 2007). Finally, VS responsiveness to monetary incentives may be more dependent on how the magnitude of a specific monetary amount is framed relative to other amounts in the task, as opposed to its absolute magnitude (Nieuwenhuis et al., 2005).

The high incidence of lifetime non-alcohol drug abuse or dependence among the SDP is potentially problematic for two reasons: First, group differences cannot be attributed solely to alcohol effects or to premorbid risk factors for alcoholism specifically. Second, these data may not generalize to alcohol-dependent individuals with no illicit drug use or with less severe addiction. We note, however, that every patient described alcohol as his or her drug of choice, and every patient evidenced a withdrawal syndrome characteristic of chronic alcohol intoxication. Also, histories of illicit drug use disorder are very common among treatment-seeking alcoholics (Walsh et al., 1991) (a majority of alcoholics in Staines et al., 2001), suggesting that these findings may generalize to alcoholics who seek treatment. We note too that the similarity between these severely-affected patients and controls in reward-anticipatory VS recruitment speaks to the degree to which the human striatum maintains its capability to mobilize behavior toward nondrug incentives despite years of chemical insult to its neurocircuitry.

Finally, we caution that: 1) our reliance on a brief NEO facet to assess impulsivity was likely inferior to use of a fuller psychometric instrument to measure subcomponents of impulsivity, 2) these findings in recently-detoxified inpatients may not generalize to individuals with histories of SD who are in extended abstinence, 3) fMRI findings using an abstract reward like money may not generalize to use of a primary nondrug reward like fruit juice (Berns et al., 2001), and 4) further validation of the ISH in SD by paradigms like the MID will likely require examining VS responsiveness to iconic cues that signal potential for actual drug delivery. Future research could modulate task parameters and reward modalities to further characterize alterations in incentive neurocircuitry in SD.

Conclusions

The present paradigm, with its jittered design, provides initial evidence for exaggerated limbic responses to gains, losses, and reward outcome deferrals in treatment-seeking substance-dependent individuals. We posit that these differences reflect a pathophysiological alteration in neurocircuitry related to learning and affect, and likely result from some combination of either premorbid externalizing behavior traits and/or chronic drug-induced neuroadaptations. For example, adults with ADHD also had greater frontocortical responses to notification of gains (Strohle et al., 2008).

Within the framework of motivation-based theories of SD vulnerability, these findings indicate that SDP differ not in their VS response to cues to respond for nondrug reward, but instead show exaggerated VS responses to reward delivery and reward omission. The general similarity between controls and SDP in VS response to nondrug reward-predictive cues does not support the RDS hypothesis. Rather, these data suggest two other possibilities: 1) Increased salience of drug-predictive cues alone (per the ISH) may be sufficient to orient behavior toward drug-taking in that recruitment of VS circuitry by cues for general nondrug rewards appears to be essentially intact. 2) A physiological signature of a core externalizing behavior trait that ostensibly accounts for the comorbidity between disruptive behavior disorders and SD in twin studies (Kendler et al., 2003; Slutske et al., 1998) might be detectable in incentive fMRI paradigms— not in VS recruitment by reward-predictive cues, but in the VS response to *deliveries or omissions* of rewards. Finally, the correlations between NEO-impulsiveness and each of NAcc and mFC activation by

rewards, and between NEO-neuroticism and insula activation by losses, provide impetus for future investigations of limbic recruitment by MID tasks as a neurophysiological signature of individual differences in either impulsivity or in affective reactions to positive and negative incentives — where these traits would be assessed by specialized psychometric measures.

Acknowledgments

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2008.06.035.

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